June 13, 1996

MEMORANDUM

SUBJECT: Final Office Policy for Performing Acute Dietary Exposure Assessment.

FROM: Debra Edwards, Ph.D., Acting Deputy Director
Health Effects Division (7509C)
Office of Pesticide Programs

TO: CBTS, CBRS, DRES, and RCAB Staff

Enclosed is a copy of the final policy which describes how OPP currently performs acute dietary risk assessment (Tiers I and II). The policy also outlines proposed future refinements to our current policy (Tiers III and IV). The policy has been reviewed by the SAP in September, 1995.

Attachment

cc: Stephanie Irene
Penelope Fenner-Crisp
Lois Rossi
Steve Johnson
Anne Lindsay
Bill Jordan
Richard Schmitt
HED Branch Chiefs

ACUTE DIETARY EXPOSURE ASSESSMENT
Office Policy
June 1996

Purpose

The purpose of this guidance document is to outline how OPP performs acute dietary exposure assessments. This document is for internal use and reflects current policy, reviewed by the SAP in September 1995.

Background

OPP intends to use a tiered approach to determine acute dietary exposure associated with pesticide use. The steps in the analysis proceed from more to less conservative assumptions. The tiered approach is considered the most efficient means of exposure assessment both for the Agency and Industry, matching the level of Agency and Industry resources used to the level of risk concern. For Tiers 1 and 2, no additional data will be required of the registrant; the registrant will be required to mitigate any unacceptable risk from Tier 3 analyses and, at their own option, may generate additional single serving size[1] (Tier 4) residue data. Analysis proceeds only to the step at which no risk concern is indicated. Selection of an MOE that triggers concern is tied to the nature of the adverse effect under consideration. Both individual and population risk will be considered in regulatory decision-making.

Currently, the Agency performs only Tier 1 and 2 acute exposure assessments. The future addition of Monte Carlo[2] analysis capability will allow the use of Tier 3 and 4 acute exposure assessments.

[1] "single serving size" - individual pieces of a commodity for which one discrete piece constitutes a serving (such as a single apple or single banana)

[2] A Monte Carlo analysis creates a joint distribution of two variables, in the case of DRES, by randomly pairing a distribution of residue chemistry data with a distribution of food consumption data, to create a representation of the actual exposure distribution.

Tiered Acute Exposure Assessment Overview

- Tier 1, using a single high end residue estimate and a distribution of consumption data, is inexpensive and the least resource intensive but gives only an upper bound (worst-case) estimate of acute exposure.

- Tier 2, the same as Tier 1, except using a single average residue data point for commodities which are typically mixed, requires minimally more effort than Tier 1, but provides a more realistic estimation of exposure by considering average anticipated residues for food forms that are typically mixed prior to consumption.

- Tier 3, using a distribution of residue data points as well as a distribution of consumption data points, requires additional Agency review time, but provides a more realistic estimation of acute exposure than Tier 2.

- Tier 4, using a distribution of residue data points from single serving size samples, is the only method which requires additional residue data from the registrant. It requires additional and expensive residue data, extensive Residue Chemistry and DRES review time, but provides the most representative exposure picture. However, it may not provide a lower exposure estimate than Tier 3.

Procedure

- Tier 1 uses a single high end residue estimate (usually the tolerance) together with a distribution of consumption values to estimate single-day exposure. This tier assumes the following:

  - All commodities which have a tolerance for a pesticide contain tolerance level pesticide residues (or the highest residue found in a field trial).

  - If residue data for the edible portion are reported in the field trials, the residue estimate for the edible portion is taken from the highest residue found in field trials conducted at the maximum use pattern on the label.

- The tolerance, or maximum legal level of a pesticide in or on a human food or animal feed commodity, is derived from the field trial composite sample[3] exhibiting the highest residue.

- 100% of the crop is assumed to be treated.

- Tolerances/residue estimates for "all raw agricultural commodities" in food handling establishments will be excluded from the analysis.

- Currently the exposure to consumers[4] only is calculated; non-consumers are excluded from the analysis.

◦ Tier 2 is the same as Method 1 for commodities which are commonly consumed as a "single serving size", or cannot be assumed to be mixed during processing; e.g., apples, oranges, pears, bananas, potatoes. For food forms that are typically mixed prior to consumption [grains (e.g. rice) and grain products, oils, sugars, most juices, tomato products (paste, puree, and juice), dried potatoes, soybeans, peanuts, mint oils, milk, wine, and sherry], an average anticipated residue from field trial data or 95th percentile residue from monitoring data is combined as above with a distribution of consumption data to estimate exposure.

- The high end residue for commodities consumed as a "single serving size" is determined the same way as it was in Tier 1.

- The residue estimate for raw agricultural commodity food forms that are typically mixed (e.g., rice, dry beans) is determined by averaging the residue data from field

---

[3] Composite samples are numerous pieces of a commodity which are blended together prior to analysis (such as 12 large potatoes or 24 lemons). Composite samples are collected in field trials because FDA monitoring for tolerance enforcement is done using composite samples, and the primary purpose of a tolerance is as an enforcement tool. Guidelines on the minimum sample sizes are outlined in the Codex "Guidelines on Minimum Sample Sizes for Agricultural Commodities from Supervised Field Trials for Residue Analysis", ALINORM 87/24A (1987).

[4] An individual on a given day is defined as a "consumer" if he consumed one or more of the foods for which a prior tolerance exists for a pesticide. For example, if only 1000 out of the 90,000 consumption data records include consumption of strawberries, then only those records would be used in the analysis. This was originally done to be protective of people actually consuming the commodities of concern.

trials conducted at the maximum use pattern on the label. Alternatively, the 95th percentile residue from monitoring data may be used.

- The residue estimate for food forms (processed foods) that are typically mixed is determined by using the average residue found in field trials conducted at the maximum use pattern multiplied by the average processing factor determined in processing studies. Alternatively, the 95th percentile residue from monitoring data may be used. For processed food forms that may be derived from a limited geographic region (individual farm, county), the highest average field trial (HAFT) should be used.

- In calculating the average residue, if the residue level of the pesticide falls below the estimated limit of detection (LOD) of the method, the limit of detection will be assigned. If the residue level of the pesticide falls between the estimated limit of detection of the method and the limit of quantitation (LOQ) of the method (point at which quantitative results may be obtained with a specified degree of confidence), the residue will be estimated to be the LOQ.

◦ Tier 3 combines the entire distribution of residues from field trials (composite samples) with the entire distribution of consumption data to estimate a distribution of exposure (convolution of distributions using the Monte Carlo method). Tier 3 allows the following:

- A distribution of residue data points is included for all possible commodities, which is more realistic than a single point estimate.

- If residue data for the edible portion are reported in the field trials, the distribution of residues from field trials conducted at the maximum use pattern on the label is used. If residue data on the edible portion are <u>not</u> available, the residue data points for the raw commodity may all be multiplied by the average processing factor to determine the distribution of residues for the edible portion of the raw commodity.

- For commodities which are typically mixed, in general, a point estimate will be used i.e. the average residue from field trials, multiplied by the average processing factor or the 95th percentile residue from monitoring data. As in Tier 2, the HAFT should be used for processed food forms that can be derived from a limited geographic region. However, distributions of residues will be used when it is necessary to further refine the analysis.

- Percent crop treated data are included in the equation, by assigning a probability that the residue level could be zero. However, consideration must be given to the possibility of regional outliers, where a higher percent of the crop is treated and marketed primarily within that region. Imported crops are assumed to be 100% treated unless better data are available.

- The total population is included in the assessment (consumers and non-consumers). This allows population exposure comparisons between analyses for different commodities and different pesticides.

- As data become available on variability inherent in composite sampling, monitoring data may be used in acute dietary exposure analysis for all foods.

◦ Tier 4 (optional) combines the entire distribution of residues from a well designed, statistically valid market-basket survey (single serving-size samples, i.e., not composited), with the entire distribution of consumptions to estimate the distribution of risks (also Monte Carlo method).

- The entire distribution of residue data points from the specially conducted market basket survey is used as residue estimates for commodities consumed as single servings. Single serving size samples are collected in these special surveys. The edible portion of the commodity is analyzed. Alternatively, the estimates for the whole commodity may be modified by multiplying by processing factors to determine the edible portion of the commodity.

- Individual serving size samples, e.g., individual apples, and a corresponding composite sample collected from the identical sampling site both should be analyzed. The concurrent analyses of individual units/serving portions and the corresponding composite may provide a basis on which later, independent monitoring data using composite sampling may be used by the Agency to assess acute dietary exposure. Additional guidance on the conduct of special surveys for Tier 4 will be provided as needed for each study.

Procedures for DRES portion of Acute Exposure Analysis

- Current DRES acute analysis uses the individual person-day data from a survey of food consumption, in which approximately 30,000 people were surveyed for 3 days each, approximately 90,000 person-day records. Each record contains information on the consumption of the 376 "raw agricultural commodities" (RACs) which make up the standard list of RACs in the DRES system. Data are recorded as grams of RAC eaten per kilogram of bodyweight on that day. If a person did not consume a particular RAC, the RAC is given a "missing value" in the database.

- Acute analyses use the person-day consumption data in the fundamental formula: Exposure = Residue x Consumption

$$E_i = R_i \times C_i \times 0.001$$

where

E = exposure from the pesticide on RAC 'i', in milligrams

pesticide/kilogram bodyweight/day,
R = the chemical residue on RAC 'i', in mg pesticide/kg RAC,
and
C = the consumption of RAC 'i', in g RAC/kg bodyweight/day.
0.001 = conversion from grams food to kilograms food

- In acute analyses, exposure is summed across all RACs for each person, and the distribution of exposures across the population is plotted on a histogram or table. The statistical weights assigned to each individual in the survey are taken into account.

- Acute exposure is expressed as a margin of exposure (MOE). The MOE is calculated using the equation,

$$MOE = \frac{NOEL}{exposure} = \frac{NOEL}{residue \times consumption}$$

- The magnitude of risk is generally estimated by comparing the exposure value to the highest dose level known *not* to cause effects (NOEL or other appropriate endpoint). Subgroups are of concern in acute analyses.

- Selection of an MOE that triggers a risk concern should be tied to the nature of the adverse effect under consideration and the type of study from which the NOEL is taken. Effects that are reversible may be regulated less stringently than those which are irreversible and life threatening. Dose-Response information is also a consideration.

- The acute DRES analysis does not take into account food handling establishments. We believe that the underlying assumption, that all commodities that are consumed on any given day will contain tolerance level residues of pesticides from a food handling establishment, is unrealistic. Residues resulting from pesticide use in food handling establishments are not likely to result in incidental contamination of all foods at tolerance levels on a uniform and consistent basis and not all foods consumed by an individual in a day are likely to have come from a food handling establishment.

- Future acute DRES analyses will reflect the total population and not consumers only. The population of "consumers" will be different for every analysis and the comparison of different chemicals is not appropriate with the present procedure. The inclusion of the total population in future analyses will permit comparison between commodities for any given pesticide, and also permit analysis of alternatives by comparing the risk picture between pesticides.

- Percent crop treated data will be included in Monte Carlo analyses in the form of 'zero' residue data points in the appropriate proportion, when field trial data are used. This will result in exposure estimates more nearly reflecting the actual exposure.

- Residues in water should be included in the DRES analysis, by including the MCL or monitoring data, as available. However, regional variations in exposure must be considered when characterizing population risks.